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Effect of low-dose ketamine on fetal oxidative stress: A randomized trial

Low-dose ketamine and fetal oxidative stress markers

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Abstract
Aim: In this study, we aimed to investigate the effect of preoperative low-dose (0.3 mg/kg) intravenous (IV) ketamine administration on fetal oxidative stress markers including Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), Malondialdehyde (MDA), and Ischemia-modified albumin (IMA) in patients undergoing cesarean section with combined spinal epidural anesthesia (CSEA).
Material and Methods: A total of 60 parturients aged 18–45 years, and undergoing elective cesarean section with CSEA were included. Two groups (n=30, for each group) were formed by randomization. Before the CSEA procedure, the ketamine group received an IV of 0.3 mg/kg ketamine diluted with 10 ml normal saline and the control group received an IV10 ml normal saline. Then, CSEA was performed using 1.8 ml 0.5% isobaric bupivacaine (9 mg) and 15 µg fentanyl. Immediately after delivery, the umbilical cord was doubly clamped, and a 5 ml of cord blood sample was drawn for biochemical analysis of fetal oxidative stress markers. The socio-demographic, anesthetic characteristics, and biochemical analysis results of the participants were recorded. The results were compared with appropriate statistical methods.
Results: There were no significant differences between the groups in terms of socio-demographic and anesthetic characteristics. Also, both groups had similar values in terms of cord blood GPx, MDA, SOD, and IMA levels.
Discussion: Preoperative low-dose IV ketamine administration has no influence on cord blood oxidative stress markers.

Keywords
Ketamine, Cord blood; Oxidant, Antioxidant, Cesarean Section, Anesthesia

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Introduction

In response to surgical stress, many metabolic reactions occur in the body [1]. As a result of these reactions, the maternal blood levels of oxidative products in the form of free radicals and non-radicals increase. These oxidative products formed in response to surgical stress in the mother may pass to the fetus via cord blood, cause damage to cells and tissues, and increase postoperative maternal and fetal morbidity and mortality [2-4]. In order to prevent cellular damage in the tissues, defense mechanisms called the antioxidative system activates, and harmful oxidative products are tried to be destroyed by enzymatic and non-enzymatic antioxidant systems [5]. Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) main enzymes with antioxidant activity and these enzymes protect the cells against damage [6]. Malondialdehyde (MDA) is a reactive metabolic product that occurs during lipid peroxidation and is an indicator of oxidative stress [7]. Ischemia-modified albumin (IMA), modified serum albumin is a biological marker of ischemia and is formed under oxidative stress [8]. Researchers reported the beneficial effects of some anesthesia techniques and anesthetic agents in reducing the surgery-induced inflammatory response [9-11].

Ketamine is used for induction of anesthesia with a rapid onset and short-term effect in patients undergoing cesarean section surgery [12]. Studies found that ketamine provides less fetal depression, so it may be preferred in cases of fetal distress [13,14]. Also, a systematic review [15] reported that low-dose ketamine (0.25 mg/kg) may inhibit postoperative stress response.

Based on the above findings, this present study aimed to investigate the effect of preoperative low dose (0.3 mg/kg) intravenous (IV) ketamine administration on fetal oxidative stress markers including SOD, GPx, MDA, IMA in patients undergoing cesarean section with combined spinal epidural anesthesia (CSEA).

Material and Methods

This randomized, double-blind study was approved by the Ethical Committee of Atatürk University, Medical Faculty, Erzurum, Türkiye. A total of 60 pregnant women undergoing elective cesarean section with CSEA in the Anesthesiology and Reanimation Department at Atatürk University, Medical Faculty, Erzurum, Türkiye from October 2021 to February 2022 were enrolled in the study.

A total of 60 parturients aged 18–45 years, classified as ASA I or II, and undergoing elective cesarean section with CSEA were included. Participants with a complicated pregnancy, such as fetal anomaly, hypertension, contraindications to study drugs, mul-tiple pregnancies, and coagulation abnormalities were excluded. Prior to the study, participants were informed about the study protocol, and written informed consent was obtained from every participant. Patients fasting for 8 hours before surgery were transferred to the operating room. Intravenous access was provided using a 16-gauge/18-gauge cannula and 500 ml of preloaded Ringer's lactate was administered intravenously. Oxygen supplementation of 2 L/min via a nasal cannula was given to all patients. Premedication was not applied. Before the anesthesia procedure, demographic characteristics (age, weight, height, ASA physical status), systolic and diastolic blood pressure values, and heart rate of patients were recorded. Two groups (n=40 for each group) were formed by randomization using a computer-generated table of random numbers. Patients and investigators were blinded to groups. An investigator prepared the studied drugs diluted with 10 ml of normal saline and supplied them in similar syringes. An anesthetist blinded to group allocation injected the drugs within 30 seconds before the CSEA procedure and collected intraoperative data. The ketamine group received an IV of 0.3 mg/kg ketamine diluted with 10 ml of normal saline, and the control group received an IV10 ml normal saline. Then, patients were placed in a sitting position for CSEA. After skin sterilization and local anesthetic infiltration (2% lidocaine), CSEA was performed using an 18-gauge Tuohy needle (Set for CSEA, Braun, Melsungen, Germany) in the L2-3 or L3-4 intervertebral space with a midline approach using the negative pressure method. The subarachnoid cavity was entered with a 27-gauge pencil-point needle using the needle-through-needle technique. After cerebrospinal fluid flow was observed, 1.8 ml 0.5% isobaric bupivacaine (9 mg) and 15 µg fentanyl was injected over 30 seconds. Then, the spinal needle was pulled out, an epidural catheter was advanced 3–5 cm into the epidural space. At the end of the anesthesia procedure, the patient was placed in the left supine position. A Pin-prick test was performed to assess the sensory block level. Surgery was allowed when the sensory block reached the T6 dermatome. If the sensory block was not observed within 20 minutes, 5 ml of 2% lidocaine solution was injected via the epidural catheter and these patients were not included in the study. A modified Bromage scale was used to evaluate the motor block level. General anesthesia protocol was planned for patients with three unsuccessful attempts to reach the intrathecal space. Intravenous ephedrine (6 mg) was used in case of hypotension (a 20% decrease in systolic blood pressure compared to preoperative values), and intra¬venous atropine (1 mg) was used in case of bradycardia (the HR < 45 beats/minute). Intraoperative nausea and vomiting were treated with IV metoclopramide (10 mg). Mean arterial pressure (MAP) and HR values were recorded every 2 minutes after spinal injection for 20 minutes and then every 5 minutes until the end of surgery. The operation time (the time from the beginning of the surgery to surgery end time), anesthetic complications, delivery time (the interval between the end of the spinal anesthesia procedure and delivery), and, the number of patients requiring ephedrine and atropine were recorded. Immediately after delivery, the umbilical cord was doubly clamped, and a 5 ml of cord blood sample was drawn into serum separator tubes and centrifuged at 3000 g for 10 minutes. Then, the obtained serum samples were kept at -80 OC for biochemical analysis of fetal oxidative stress markers. Also, umbilical artery blood gas values and neonatal APGAR scores at 1 and 5 minutes after delivery were recorded. After the operation, patients were transferred to the recovery room. Postoperative pain was evaluated with the Visual analog scale (VAS; 0 cm= no pain, 10 cm= worst pain). In the case of VAS > 3 in a patient, 10 ml of 0.1% bupivacaine solution was given through the epidural catheter. Anesthesia-

related side effects and sensory block time (from the spinal anesthetic injection to the recovery of T10 dermatome) were evaluated postoperatively by an anesthetist blinded to the group assignment. When the sensory block had regressed to the T10 level, patients were transferred to the inpatient service.

Biochemical analysis

Cord blood SOD levels were measured using a "Human SOD ELISA Kit" produced by Bioassay Technology Laboratory (BT LAB, Cat. No:E0700Hu, China). Cord blood GPx levels were determined via a "Human GPX ELISA Kit" produced by Bioassay Technology Laboratory (BT LAB, Cat. No.E3921Hu, China). Cord blood MDA levels were measured with a "Human MDA ELISA Kit" produced by Bioassay Technology Laboratory (BT LAB, Cat. No.E1371Hu, China). Cord blood IMA levels were determined using a "Human IMA ELISA Kit" produced by Bioassay Technology Laboratory (BT LAB, Cat. No.E1172Hu, China). All measurements were made according to the manufacturer's instructions. The SOD, GPx, IMA, and MDA levels were expressed as ng/mL, µU/mL, nmol /mL, ng /mL, respectively.

Statistical Analysis

The primary endpoint was the difference in cord blood IMA levels between groups. Sample size estimation was based on the study performed by Omür et al. [16]. To detect a 25% difference between groups in terms of IMA levels, with an α error of 0.05 and a power of 85%, it was calculated that the sample size should be 25 subjects per group (available at: http://www.stat.uiowa.edu/~rlenth/Power). Thirty patients were enrolled in each group to allow dropouts.

Statistical analysis was performed using SPSS software 12.0 (SPSS Inc., Chicago, IL, USA). The data were presented as mean ± standard deviation, median (minimum-maximum), or n (%), and $P < 0.05$ was considered statistically significant. To assess the normal distribution of data, the Kolmogorov-Smirnov test was performed. When data were not normally distributed, comparisons were done with the Mann-Whitney U-test. The Independent T test was used when comparing non-normally distributed data and the Chi-squared test was used for the analysis of categorical variables.

Results

During the study period, 90 parturients were eligible, 18 did not meet the inclusion criteria and 12 declined to participate in the study. A total of 60 parturients, who were scheduled for elective cesarean section, were recruited. The CSEA was successful for all parturients. All patients had sufficient anesthesia during surgery. Data collection was completed in 60 patients (n=30, for each group) (Figure 1).

Patients in the two groups were comparable in concerning socio-demographic, anesthetic, and surgical characteristics (Table 1).

There were no significant differences between groups in terms of mean arterial blood pressure values (Figure 2).

Patients in the control group had significantly lower heart rate values at the 4th, 6th and 8th minutes of the surgery compared to the ketamine group (Table 2). Neonatal parameters and cord blood arterial blood gas analysis results were similar in both groups. Also, both groups had similar values in terms of cord blood GPx, MDA, SOD, and IMA levels (Table 3).

Table 1. Demographic and surgical characteristics of the groups

	Ketamine group (n=30)	Control group (n=30)	p value
Age (year)	29.96 ± 4.64	31.4.09 ± 4.54	0.232
Height (cm)	161.53 ± 5.33	162.60 ± 6.57	0.493
Weight (kg)	77.50 ± 9.31	79.00 ± 11.02	0.571
Gravidity	3.56 ± 1.52	3.26 ± 1.25	0.409
Gestational week	37.66 ± 1.32	37.53 ± 0.81	0.640
Operation duration (min)	78.50 ± 26.49	74.33 ± 27.34	0.551
Delivery time (min)	13.40 ± 4.34	12.26 ± 4.47	0.324
Nausea- vomiting n (%)	2 (6.66)	4 (13.33)	0.671
Atropine requirement n (%)	0 (0)	1 (3.33)	1.00
Ephedrine requirement n (%)	15 (50)	13 (43.33)	0.796
The time to T6 level (second) med (min-max)	120 (60-300)	120 (60-420)	0.788
The time of regression to T10 (min) med (min-max)	110 (65-180)	120 (50-180)	0.799

Values are presented as an average ± SD or n (%).

Table 2. Comparison of heart rate (bpm) values among groups

Time (minutes)	Ketamine group (n=30)	Control group (n=30)	P value
Baseline	94.20±11.94	92.24±14.77	0.573
2	100.80±14.99	94.03±13.59	0.720
4	101.23±12.30	90.66±17.55*	0.009
6	102.03±11.22	93.00±13.44*	0.006
8	101.23±16.48	93.16±11.99*	0.034
10	101.10±17.03	94.23±13.50	0.089
15	97.50±14.30	93.13±15.77	0.266
20	99.03±13.67	95.23±13.35	0.281
25	96.93±11.76	95.00±13.66	0.559
30	95.73±11.75	96.10±12.61	0.908
40	94.26±12.78	94.23±10.12	0.991
60	96.26±12.19	92.63±1046	0.221

Data were expressed as mean ± SD. *P<0.05; compared with ketamine group.

Table 3. Biochemical analysis results and neonatal data in groups

	Ketamine group (n=30)	Control group (n=30)	P value
GPx (µU/mL)	278.61± 635.03	331.69 ± 1081.47	0.817
MDA (ng /mL)	19.90 ± 2049	16.53 ± 24.69	0.567
SOD (ng/mL)	46.26 ± 51.59	44.16 ± 68.37	0.894
IMA (nmol/mL)	147.60 ± 161.02	121.70 ± 189.79	0.571
APGAR score at 1 min	8.23 ± 0.66	8.51 ± 1.14	0.733
APGAR score at 5 min	9.74 ± 0.48	9.55 ± 0.71	0.903
Hemoglobin (g/dL)	15.23 ± 1.33	15.71 ± 1.62	0.207
Glucose (mmol/L)	68.36 ± 11.21	64.60 ± 9.12	0.159
Lactate (mmol/L)	2.96 ± 1.57	2.62 ± 0.94	0.310
Umbilical artery pH	7.30 ± 0.07	7.31 ± 0.05	0.687
Umbilical artery PCO2	46.59 ± 9.51	43.49 ± 8.00	0.177
Umbilical artery PO2	30.21 ± 10.41	30.82± 10.80	0.825
Umbilical artery HCO3	22.22 ± 1.45	21.66 ± 1.94	0.211
Umbilical artery base excess (min/max)	-3.00/1.50	-3.54/1.81	0.219
Fetal weight (gram)	3055.66 ± 463.36	3144.06 ± 442.57	0.453
Male/Female	15/15	21.9	0.114

Values were expressed as mean ± SD or min-max. GPx: Glutathione peroxidase, MDA: Malondialdehyde, SOD: Superoxide dismutase, IMA: Ischemia-modified albumin

Figure 1. Flow chart of study participants

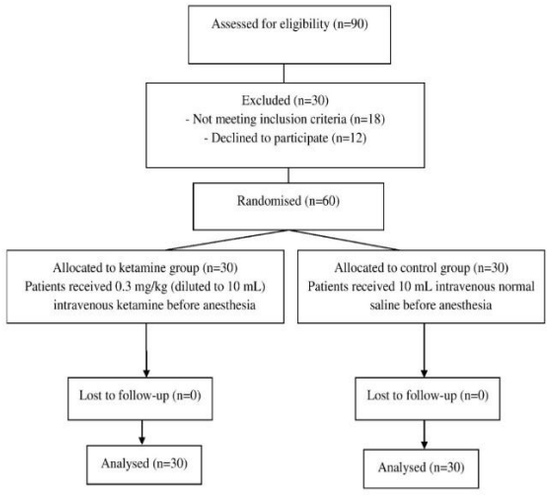
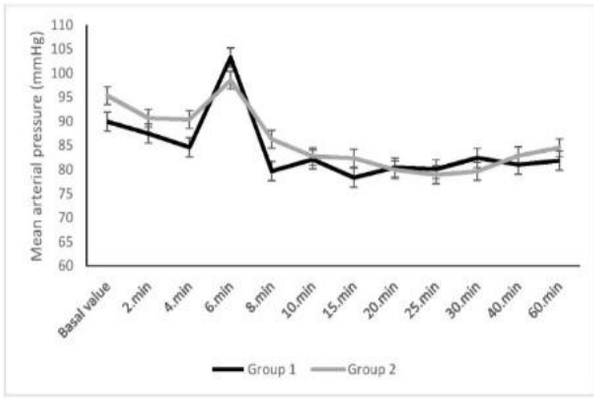


Figure 2. The changes in mean blood pressure values in groups



Discussion

This present study aimed to investigate the effectiveness of preoperative low-dose intravenous ketamine (0.3 mg/kg) in attenuating oxidative stress response in the fetus in patients undergoing elective cesarean section with CSEA. We observed similar cord blood GPx, MDA, SOD, and IMA levels in the ketamine group in comparison with the control group.

Surgical stress increases cytokine release and leads to an increase in oxidative products. It was reported that these oxidative products increase postoperative maternal and fetal morbidity and mortality [1-4]. For this reason, researchers investigated the effects of different anesthesia methods and drugs on the surgical stress response. In a study, Vosoughian et al. [11] compared maternal serum levels of interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in general and spinal anesthesia among patients undergoing cesarean section. They reported postoperative higher IL-6 and TNF-α levels in the general anesthesia group compared to the spinal anesthesia group. They concluded that the spinal anesthesia technique may be a better option for reducing maternal surgical stress in patients undergoing cesarean section. In another study, Kang et al. [17] reported that Dexmedetomidine administration during surgery reduces cytokine release and postoperative leukocyte and CRP levels in patients undergoing laparoscopic cholecystectomy.

Ketamine, an N-Methyl-D-Aspartate (NMDA) receptor antagonist is frequently used for induction and maintenance of anesthesia. Experimental studies revealed the anti-inflammatory effects of ketamine [18,19]. Spencer et al. [20] reported that sub-anesthetic doses of an IV ketamine infusion reduce TNF-alpha levels in both male and female rats. In an in vivo experiment, Zhou et al. [21] revealed the protective effect of ketamine against hypoxia-induced injury in human umbilical vein endothelial cells. Therefore, we hypothesized that preoperative low-dose IV ketamine might reduce the surgical stress response in the fetus. For this purpose, we compared the effects of adding preoperative small-dose ketamine during CSEA on cord blood GPx, MDA, SOD, and IMA levels in patients undergoing cesarean section. We reported no differences between groups in terms of these oxidant and antioxidant parameters. Inconsistent with our results, Senapathi et al. [10] reported that low-dose intravenous ketamine decreases maternal CRP levels in patients undergoing emergency cesarean section under spinal anesthesia. Gokcinar et al. [22] investigated the anti-inflammatory and antioxidant efficacy of ketamine in a rat model of acute lung injury. They reported that ketamine decreases oxidative stress and inflammation in both plasma and lung tissue. Xingwei et al. [23] showed that low-dose ketamine before general anesthesia protects organs from potential oxidative damage and inflammation caused by pneumoperitoneum. However, this present study failed to demonstrate the antioxidant activity of ketamine in cord blood. In this instance, we speculated that the time might not enough for the ketamine to cross the placenta and reach the cord blood. But it is known that showed that ketamine rapidly passes the placenta and that ketamine levels in cord blood reach the same levels as in the mother's venous blood approximately one and a half minutes after IV ketamine injection [24].

Ischemia-modified albumin has been reported to be an important indicator of hypoxia, ischemia, and oxidative stress response. Omür et al. [16] have suggested that different anesthesia techniques may have different effects on cord blood IMA levels in patients undergoing cesarean section. They reported similar values in IMA levels during cesarean section with general anesthesia or CSEA. Consistent with these results, we observed similar cord blood IMA levels in the ketamine group compared to the control group.

This is the first study in the literature evaluating the effect of preoperative low-dose ketamine on cord blood SOD, GPx, MDA, and, IMA levels. There is a limitation in this current study. It would be interesting to measure cord blood oxidant and antioxidant levels in different groups, such as preeclampsia or diabetes, following administration of preoperative low-dose ketamine. Comprehensive studies including different patient groups may be planned.

Conclusion

This present study showed that preoperative low-dose IV ketamine administration has no influence on cord blood oxidative stress markers. Further studies need to evaluate

the effects of low-dose ketamine on cord blood oxidant and antioxidant parameters.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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